Catalase comparable to the vitamin E treatment. DISCUSSION/SIGNIFICANCE OF FINDINGS: If addition of apelin causes an antioxidant response in all three cells types, this can build on evaluation of the APJ system as a therapeutic option for those with CKD and CRS4 to minimize both inflammatory and oxidative stress. With the data gathered here, we expect to recreate the results in a CKD rat model that highlights these same manifestations.

25380

Cholecystokinin-B Receptor Mediates Growth of Hepatocellular Carcinoma*

Martha Dee Gay, Anita Safronenka, Hong Cao, Robin Tucker, Narayan Shivapurkar and Jill P. Smith
Department of Medicine and Pathology, Georgetown University, Washington DC, USA

ABSTRACT IMPACT: Cholecystokinin-B Receptor Mediates Growth of Hepatocellular Carcinoma with the use proglumide. Proglumide is a non-selective antagonistic drug therefore, strategies that block signaling at the CCK-BR may provide to be a novel therapeutic option for Hepatocellular Carcinoma treatment OBJECTIVES/GOALS: Cholecystokinin (CCK)and gastrin mediate the growth of Hepatocellular Carcinoma (HCC) through CCK-R and interruption of this signaling pathway could decrease HCC. CCK-Receptors are overexpressed in HCC and proliferation may be mediated through CCK-B. Blockade of the CCK-BR with proglumide decreased both growth in vitro and tumor growth in vivo. METHODS/STUDY POPULATION: RNA was extracted from murine Hepa1-6, RIL-175 and human HepG2 cells and was evaluated by qRT-PCR for expression of CCK-AR, CCK-BR and gastrin. CCK-R protein expression was analyzed by flow cytometry. HCC cells were treated in vitro with CCK peptide, the CCK-AR antagonist or the CCK-BR antagonist. Proliferation of selective CCK-R KO cells was compared to that of wild-type cells. To determine the effect of a CCK-R antagonist on tumor growth in vivo two cohorts of mice bearing subcutaneous Hepa1-6 or RIL-175 HCC tumors were treated with an oral bioavailable CCK-R antagonist proglumide or untreated water for 3-4 weeks. The mice bearing Hepa1-6 tumors were placed on a high-fat diet to raise blood CCK levels. Mice bearing RIL-175 tumors were fed standard chow to determine if proglumide could block autocrine growth by gastrin. RESULTS/ANTICIPATED RESULTS: The mRNA expression of CCK-AR, CCK-BR and gastrin were increased 80-90-fold in all HCC cell lines compared to that of normal liver. CCK-BRs were detected on >85% of the cells by flow cytometry. CCK peptide (1nM) stimulated HCC growth in vitro in both wild-type cells and in CCK-AR KO cells but not in CCK-BR KO cells. CCK-BR antagonist blocked CCK-stimulated growth in vitro but the CCK-AR antagonist did not, suggesting that the CCK-BR was responsible for mediating proliferation. In vivo tumor growth was significantly reduced with proglumide treatment by 70% ($p<0.05$) in Hepa1-6 and by 73% ($p<0.001$) in RIL-75 tumors, respectively. DISCUSSION/SIGNIFICANCE OF FINDINGS: CCK-Rs are overexpressed in HCC and proliferation appears to be mediated through the CCK-BR. Downregulation with CRISPR Cas9 or blockade of the CCK-BR with an antagonist decreases growth in vitro and proglumide therapy decreases tumor growth in vivo. Strategies that block signaling at the CCK-BR maybe a novel therapeutic option for HCC treatment.

27558

Obeticholic acid (OCALIVA ®) protects against 2,8-dihydroxyadenine nephropathy in mice

Bryce Jones[1], Carlos Benitez[1], Idalia Cruz[1], Komuraiah Myakala[1], Xiaoxin Wang[1], Andrew Libby[1], Emma Rowland[1], Ryan Kurtz[1], Avi Rosenberg[2] and Moshe Levi[1]
[1]Georgetown University and [2]Johns Hopkins University

ABSTRACT IMPACT: This work may lead to new treatments for crystalline nephropathies. OBJECTIVES/GOALS: This study investigated obeticholic acid (OCALIVA ®) as a potential treatment for 2,8-dihydroxyadenine (2,8-DHA) nephropathy using a mouse model. The treatment was investigated in both sexes at two timepoints. METHODS/STUDY POPULATION: Male and female C57BL/6J mice (12 weeks of age) were fed chow (Research Diets D19120401i) or chow admixed with adenine (0.2% w/w) ad lib for either 3.5 or 7 weeks. Mice were treated with either vehicle (corn oil) or obeticholic acid (10 mg/kg BW) by gavage 5 days per week. Each of the 16 combinations of sex/diet/timepoint/treatment groups had an $n = 6$ (96 mice in total). Food and body weights were measured twice per week, and 24-hour urines were collected prior to euthanasia. Serum and organs were collected and processed for biochemical and histopathological analyses. RESULTS/ANTICIPATED RESULTS: At both the 3.5-week and 7-week timepoints, dietary adenine robustly increased BUN and serum creatinine compared to control diet in vehicle-treated male and female mice ($P < .01$, all comparisons). At the 3.5-week timepoint, obeticholic acid reduced BUN in male ($P < .05$) but not female adenine mice. Obeticholic acid did not affect serum creatinine at this timepoint. At the 7-week timepoint, obeticholic acid reduced BUN in female ($P < .05$) but not male adenine mice. At the 7-week timepoint, obeticholic acid reduced serum creatinine in both male ($P < .05$) and female ($P < .01$) mice. Biochemical and histopathological analyses are ongoing, and we anticipate that the results will agree with the serum chemistries. DISCUSSION/SIGNIFICANCE OF FINDINGS: Obeticholic acid is FDA-approved for primary biliary cholangitis, and it is in clinical trials for several other hepatobiliary diseases. Although currently untested in humans, it is nephroprotective in many preclinical models of kidney disease. This study is the first to investigate obeticholic acid in a model of crystalline nephropathy.

32219

Differences in cell death in methionine versus cysteine depletion

Katherine F. Wallis and Isabelle R. Miousse
University of Arkansas for Medical Sciences

ABSTRACT IMPACT: Reducing methionine levels has repeatedly been shown to reduce cancer growth in vivo, while at the same time increasing lifespan in healthy animals. However, the mechanisms behind the beneficial effects of methionine restriction are currently unknown. OBJECTIVES/GOALS: We hypothesized that comparing the response of a cancer cell line to depletion of the amino acids methionine and cysteine would give us insight into the critical role of these two closely related amino acids in cancer, and help advance methionine restriction on the translational science spectrum. METHODS/STUDY POPULATION: We used the human

https://doi.org/10.1017/cts.2021.427 Published online by Cambridge University Press